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13. Abstract ***(Maximum 200 Words)*** *(abstract should contain no proprietary or confidential information)*

This project was designed to test a new method for the evaluation of lesions suspected as possible cancers after their initial detection. Electrical Impedance Imaging (EII) is a novel method for the evaluation of breast lesions that relies on measurements of the electrical impedance and capacitance of breast tissues. It showed, in previous trials, good ability to distinguish benign and malignant lesions. The system received FDA approval 4/16/99.

The work on this project was delayed because we have not yet received approval from the US Army to start the clinical trial. New information also indicates the need for protocol modification and we have submitted the new protocol for approval.

Because the system is FDA approved, we have been using it both clinically and in other clinical trials and have discovered that the system is not ready for the type of use originally proposed. The main problem is that the system has a very large number of false positive findings, that is findings that are positive by EII criteria, but are not cancer. In some breasts four or more such false positives can be found.

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Abstract

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Introduction:

Electrical Impedance Imaging (EII) of the breast is a novel method for distinguishing benign and malignant breast lesions. This project was designed to add EII to an existing protocol, the Coordinated Approach to breast Cancer Diagnosis (CABCAD) that started in 1997. That project was a complex project in which women with relatively low suspicion of breast cancer, but for whom breast biopsy had been advised, underwent a series of both usual and special studies to determine if any study or any combination of them would allow the biopsy to be avoided. The goal was to find studies or combinations of studies that had a high negative predictive value. The basic studies to be performed were as many as possible of the following: Mammography, MRI, and 99mTcSestamibi (at that time not FDA approved, but approval was subsequently given). In addition, the project was designed to allow the incorporation of additional special studies of new methods for breast cancer diagnosis that could be added or dropped as the basic study progressed. Two methods were dropped (breast visualization with a small breast sized gamma camera and sonoelastography). In 1999 we applied to the US Army for additional

funding for a study of a new method called Electrical Impedance Imaging to be incorporated into the study. This was approved for funding, but for various reasons, we were unable to establish US Army approval for use of this FDA approved method into the study. For this reason, the starting of this project was delayed.

Body of Report

Because of delays in obtaining US Army approval for the clinical trial, we do not have results from this clinical trial to report. During the delay, however, we had this FDA approved machine in our clinic and discovered that it was also pre-mature to incorporate its use into CABCAD. We performed preclinical studies and we worked with this system on clinical patients and as part of other research protocols. The pre-clinical work was an extensive testing of the reliability of measurement of the electrical signals. Our internal report of this is provided in the appendix. In brief summary, what we found was that with the initial system provided by the manufacturer, there was wide variability in the signal measured from each of the individual elements of the transducer probe. We also constructed several phantoms and studied their measurement characteristics. After this work, we expressed some doubt to the manufacturer who promised us a newly redesigned probe.

Once the new probe was delivered and since the machine was FDA approved and in our clinic, we started to look at clinical patients and at volunteers in other (non-DOD) research studies with the approval of the Georgetown IRB. What we found is that even with the new probe, the system as had adequate, but lower than expected sensitivity and also much poorer specificity than originally reported by the company. We found that the original system (with the new probe added) provided false positive findings in almost all women studied and missed many cancers. Of greatest concern was that the system had many false positive findings in women in whom we could find no abnormality on mammography or MRI. Our original hypothesis for this IDEA proposal was that we would characterize the false positive lesions (ie there would be lesions that were not cancer and we would characterize them). Instead, we found that there was nothing there that we could characterize. On discussing this with the Company, they assured us that new software would solve the problem; we decided to wait for these new developments. I did not consider it appropriate at that point to test in women a system that clearly did not have adequate negative predictive value to be of use to be relevant to the CABCAD project.

The company delivered several upgrades of both hardware and software. In September, 2000, the company delivered the latest version of software improvements that for some reason did not work as described in our machine. After several months of work with the company, the system did start working as designed (around February, 2001), but by then the underlying CABCAD study had completed its clinical trial and only data analysis was being performed.

It was clearly inappropriate to incorporate the system as a component of CABCAD because of the machine was not ready for clinical use (despite its FDA approval). In

using the system in other projects and as part of clinical care, we determined that the main problem with the system was the very large number of false positive findings (in some women, there were three to four false positive findings in the absence of any lesion being visible on mammography and MRI). The problem that needed to be addressed was the cause of the false positives. We therefore rewrote the research protocol to allow us to study this problem. This new protocol has been submitted to the US Army and the Georgetown IRB for review and is currently being evaluated.

Information about EII that has become available since the original submission

There has been one recent publication on the use of the EII system. Malich studied 52 women with sonographically and or mammographically suspicious findings. There were 29 malignant and 29 benign lesions in these women (some women had more than one lesion). All patients were also imaged with MRI. Two different methods of EII were used, (1) targeting the specific lesion and (2) surveying the breast. When specific lesions were targeted, this study showed a positive predictive value of 93% and a negative predictive value of 73%. While this study would seem very promising, the problem is that the lesions in the study were quite large. The malignancies averaged 17 mm in size and none of the invasive cancers were less than 1 cm. More important is that in the surveys of the breasts there were 47 spots in 52 patients. 22 of 29 malignancies were identified, but 25 of the spots were false positives. This study shows that the system does detect many cancers. At the same time a system where more than ½ of the lesions detected are not cancer is in need of further study and further improvements.

System changes since FDA approval was granted

Our group started with the EII system design approved by the FDA. Our preliminary tests of this system demonstrated a large amount of detector inhomogeneity. There was also a very large inconsistency of measurement seen. Our investigating of the electrical system demonstrating this is in the attached report.

Subsequent to FDA approval, the manufacturer provided us with a new probe for recording the information. The system has also had two software upgrades. The most recent incorporate a neural network approach to analyzing the data. The manufacturer is also developing a new processing board that will permit the incorporation of higher electrical frequencies into the analysis of lesions. Our current impression of the latest system is that the sensitivity has increased, but at the same time the number of false positive detections has also increased.

The variable resistance of the skin as a barrier to success

Electrical contact with the skin is a major limitation of the use of EII. There are several problems. First, the standard coupling gel that is used has a propensity to create artifacts from air bubbles that accumulate in it during scanning. While these can be controlled, we have tried 4 alternative coupling agents (different gels and skin lotions), but have not yet found a solution to the problem. Second, the electrical resistance of the skin is non-

uniform. This is a topic we intend to study further once we have US Army approval to proceed to human studies. Third, moles, insect bites and other focal skin lesions also show increased EII activity.

Description of new protocol submitted to the US Army for approval

We have submitted a new protocol to the US Army as a modification of the existing protocol. In this new protocol, we will focus specifically on trying to understand the nature of the many false positive results that occur with this system. Initially, we thought that the false positive results were caused by benign lesions, but in most cases we find no focal abnormality in the women with these false positive findings when we correlate their findings with MRI and mammography. They occur in women with large amounts of fatty replacement and in women with glandular breasts. They occur in pre and post menopausal women. The new protocol is attached.

Key Research Accomplishments

We have demonstrated the inaccuracy of measurement of the original system as provided by the manufacturer and as approved by the FDA. This is documented in the attached internal report.

Both because we did not have US Army approval for human use and also because we did not consider the system ready for clinical research we do not have systematically acquired clinical research data. The system did not perform as originally indicated by the company's report to the FDA. It has undergone progressive improvement.

We have submitted a new research protocol to the Georgetown University IRB and to the US Army for review that we believe will provide more useful information.

Reportable Findings

None at this time

Conclusions

The initial system, as delivered to us, was not suitable for clinical use. With the current system, we have studied eight patients with cancer, all of whom were positive. At the same time almost every woman we have studied who did not have cancer has also had at least one positive finding on EII. Clearly the system's sensitivity shows that it could have a major role in breast cancer diagnosis, but in its current configuration, it still needs further improvement. The main focus of our future research with this system will be to gain better understanding of the causes of the false positive findings by correlation with other imaging methods used in the same patients. We are hopeful that the new protocol will receive rapid approval both by the Georgetown IRB and the US Army Human Subjects Review

Reference

Malich A, Fritsch T, Anderson R, Boehm T, Freesmeyer MG, Fleck M, Kaiser WA. Electrical impedance scanning for classifying suspicious breast lesions. First results. 2000. Eur Radiol 10: 1555-1561.

Appendices

1. Report on the electrical properties of the TransScan Electrical Impedance Imaging System (Internal document Georgetown University Medical Center).
2. Revised Protocol submitted August, 2001.

Investigation of TransScan

A Study of Electrical Impedance Mapping in the Detection of Breast Cancer

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Abstract

TransScan is a device that maps electrical impedance distribution over an organ. The application of interest in this paper is in the area of breast cancer detection. Described are experiments performed so as to learn more about TransScan. The experiments entail creating a phantom to mimic breast tissue of differing densities and to learn more about the mechanics of the system. Upon upgrading the tool, in the near future, continued experiments in a like manner will be done. Eventually, TransScan could possibly be used as an adjunctive test to mammography.

Background

Breast cancer is the second leading cause of death in women in the United States, exceeded only by lung cancer. In women of the age group 40-55 years old, breast cancer is the number one cause of death. In 1997, 43,900 women succumbed to breast cancer.

As is the case in all cancers, the earlier cancer is detected, the better the chances of survival. In the case of breast cancer, the 5-year survival rate when cancer is detected and treated when it is localized to one area is 96.8%. As the cancer spreads, the survival rate becomes increasingly lower. When breast cancer is detected at younger ages (younger than 45 years), there is only a 79% survival rate (most likely due to the fact that the tumor attacking is more aggressive than most). This survival rate increases with age.[i]

Currently, as per the screening guidelines set up by the American Cancer Society, mammography is the gold standard by which breast cancer is screened. Nonetheless, mammograms miss up to 25 percent of breast cancers in women in their forties and about 10% of cancers in women aged 50 and older. All women with abnormal mammograms undergo follow-up procedures. 97% of women with abnormal mammograms yield false positives after follow-up

examination. The same is true for 86% of women aged 50 and older.[ii] The reason for the discrepancies between detection for older and younger women is the difference in radiographic density that changes with age. Women who have gone through menopause have more fatty tissue and less epithelial tissue in their breasts – they are less radiographically dense. In general, women in the 30-39 year age group have breasts that are 60% radiographically dense. In the 50-59 year age group, the breasts are more than 20% dense. In the 80-89 year age group, the breasts are approximately 10% dense.[iii]

One of the various new methods that have been devised to correct for failings in mammography is an instrument called Trans Scan. The mechanism by which Trans Scan operates is non-invasive. Through utilization of a hand-held probe, it maps, in real-time, electrical impedance distribution over biological tissue. It is hoped that this instrument, just recently approved by the FDA, will be used as an adjunct to mammography. Following are the results of a double-blinded study performed by TransScan R&D, Ltd. (table 1 & 2). The study was performed internationally in seven clinical centers in the US, Europe and Israel in 1997. Each patient examination (whether clinical, mammogram, or TransScan) was performed without knowledge of the results of other tests.

	Sensitivity	Specificity
TransScan Alone	69%	45%
Mammography alone	82%	39%
TransScan and Mammography	86%	51%

Table 1

Furthermore, the same study showed a correlation between age and TransScan sensitivity and specificity.

	Sensitivity	Specificity
Under 50 yrs	81%	76%
Over 50 yrs	76%	66%

Table 2

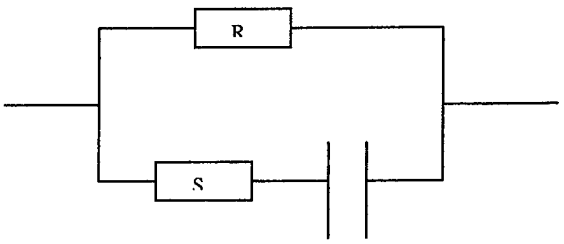
TransScan relies on a theory of biological tissues that describes their electrical properties. Like all things, biological tissues provide resistance to electricity. The degree to which the tissue is a conductor of electricity is dependent upon the water and electrolyte content of the cells. Some cells in body tissue have a unique feature in that they are surrounded by membranes and, thus, have a degree of capacitance. A cell consists of a non-conductive lipid (a dielectric) surrounded by 2 layers of protein. These layers of protein act as a semi-permeable membrane and maintain an ionic gradient across the cell. The ionic gradient creates an electrical potential across the cell. When cells are exposed to an alternating current, the cells act as capacitors – they hold charge due to the dielectric effect.

In general, as per the theory described above, healthy cells are ones in which the concentration gradient is well maintained – that is, the integrity of the membrane is good. Healthy cells have larger reactance values and lower capacitance. Lean tissues contain a large amount of water and offer poor resistance to electricity. Fatty tissue, while having no contribution to capacitance, are not good conductors as there is very little water or electrolyte content in their cells. The same is true for bones.[iv] As for cancerous tissue, one would expect an increase in conductivity and in the dielectric constant. The capacitive reactance of cancerous tissue would be higher.[v] The impedivity that results when biological tissue is exposed to an alternating current can be used to characterize biological tissue.[vi] Figure 1 describes bioimpedance for most tissues[vii]:

$Z = R_s - jX_s = Z_\infty + R_2 / [1+(\omega \Im_m j)^\beta]$

where $Z_\infty = \lim Z(\omega \rightarrow \infty)$
$Z_0 = \lim Z(\omega \rightarrow \infty)$
$R_2 = Z_0 - Z_\infty$
$\Im_m$ = time constant
β = degree of deviation from Debye type (β=1)

where, theoretically, a cell is represented by:



R= extra-cellular fluid
S= intracellular fluid
C= cell membrane
f_m(characteristic frequency) = $1/2\pi C(R+S)$

Figure 1

The aforementioned properties are the principles by which the development of TransScan is guided. TransScan uses a non-invasive, multi-element probe that detects changes in electrical impedance. The multi-element probe is used so as to ensure uniform and repeatable contact with the skin. In using an analysis of electrical impedance to detect cancerous tissue, TransScan attempts to create a map that gives the maximum contrast between malignant and non-malignant tissues. Specifically, the images that are produced by TransScan are maps of changes in conductivity and capacitance. These are measured by comparing the amplitude and phase of the signal received by the sensing elements. Clinically, these values of capacitance and conductivity have some significance and can be used to interpret the maps that are produced.

Thus, armed with information concerning the basics of biological tissue, the workings of TransScan and the fallibility of mammography, we set about learning about the instrument in as much detail as possible. This endeavor was driven by the notion that, eventually, TransScan can be used in the United States as an adjunctive means of detection to mammography.[viii]

Procedure and Results:

Effectively, our goal through these series of experiments was to learn as much about the tool as possible. This, in our minds, required us to come up with a phantom to mimic breast tissue. Such a thing would allow for a reliable standard by which one could measure the results from the instruments. Unfortunately, the version of our tool was not the most recent, this should be kept in mind while reading this analysis.

Our first attempt at gaining an understanding of the instrument was by using it upon our own skin. In doing that, we were able to resolve two points: 1. Standard values of conductivity

and capacitance in human tissue as our particular instrument registered them 2. That path length in the body has little effect on the absolute values gathered from the tool.

Measurements were performed using TransScan on our own body parts. The hand that held the source was constant throughout, and the probe was moved from body part to body part. Tables 3-6 display the results.

Electrode in left hand, Right fingers (Table 3)

TRIAL	COND (μSM)	CAPAC (ηF)
1	2.33	3.13
2	4.50	4.76
3	3.58	3.59
4	4.39	4.39
5	4.59	5.05
6	5.36	5.25
7	4.89	5.33
8	3.67	4.26
9	4.91	4.77
10	3.17	3.57
Avg.	4.14	4.41
Std. Dev.	0.930	0.76

Electrode in left hand, left fingers (table 5)

TRIAL	COND (μSM)	CAPAC. (ηF)
1	3.21	3.62
2	2.78	3.37
3	3.29	2.70
4	3.10	2.54
5	3.17	2.41
6	2.28	2.36
7	3.04	2.30
8	3.16	2.24
9	3.23	3.18
10	3.19	2.24
Avg.	3.05	2.65
Std. Dev.	0.30	0.44

Electrode in left hand, right arm (table 4)

TRIAL	COND (μSM)	CAPAC. (ηF)
1	1.79	3.65
2	1.43	3.55
3	1.80	3.88
4	2.41	4.75
5	1.39	3.78
6	2.08	4.59
7	2.13	4.29
8	2.18	4.57
Avg.	1.90	4.13
Std. Dev.	0.36	0.47

Electrode in left hand, left arm (table 6)

TRIAL	COND (μSM)	CAPAC. (ηF)
1	1.53	4.73
2	1.52	4.36
3	1.54	4.36
4	1.55	4.40
5	1.63	4.44
6	1.56	4.46
7	1.50	4.36
8	1.57	4.43
9	1.49	4.38
10	1.49	4.45
Avg.	1.53	4.437
Std. Dev.	0.043	0.110

As we were taking measurements, we found that consistencies within one set of tests would increase as time went on. That is, the initial tests were quite inconsistent, whereas the final tests became more consistent (the first test was that of right fingers, the last was the left arm examination). Furthermore, the results were indicative of the fact that path length has little effect on the values of conductivity and capacitance one gets from the instrument. The most reliable comparison to support that point is between right and left arms.

Once these notions had been settled, the next step was a more concrete one towards finding a phantom for breast tissue. In finding a phantom, one needed to find something with comparable capacitance and conductivity. In the case of capacitance, it meant finding something with both a significant capacitance and a large dielectric constant, both characteristics of biological tissues. To suit our needs, we needed a phantom over which we had control of its conductivity. According to DS Holder et al, a combination of cucumber and a potassium salt solution had a desirable effect inasmuch as the dielectric constants came close to that of human tissue. This provided a guide to our consequential experimentation.

We divided our search for a phantom into two areas. One was a search for test objects with which to vary capacitance, the other was a search for a medium, though which conductivity could be varied.

Media

In finding the proper medium for the phantom, media with stable impedance changes and a variable conductivity were looked for. These criteria were met by gelatin (we used store-bought Jell-O). The gelatin's conductivity was changed by adding different amounts of salt to change the concentration (tables 7-9). Capacitance was not expected to change or to even register. The values for capacitance shown in the table are default values, indicative of the

computer's inability to compute capacitance accurately, since the capacitance was most probably an infinitely small amount.

Plain gelatin (table 7)

TRIAL	COND (μSM)	CAPAC. (ηF)
1	29.67	0.440
2	26.00	0.440
3	28.12	0.440
4	23.38	0.440
5	24.60	0.440
6	22.44	0.440
7	22.86	0.440
8	23.53	0.440
9	23.61	0.440
10	23.49	0.440
Avg.	24.77	0.440
Std. Dev.	2.41	0.00

<0.2% NaCl concentration in Gelatin (table 8)

TRIAL	COND (μSM)	CAPAC. (ηF)
1	24.07	0.440
2	21.71	0.440
3	20.72	0.440
4	20.72	0.440
5	20.84	0.440
6	20.16	0.440
7	21.29	0.440
8	23.04	0.440
9	22.62	0.440
10	23.044	0.440
11	22.62	0.440
12	21.90	0.440
Avg.	21.71	0.440
Std. Dev.	1.22	0.00

~0.2% NaCl concentration in Gelatin (table 9)

TRIAL	COND (μSM)	CAPAC. (ηF)
1	24.76	0.440
2	23.10	0.440
3	24.64	0.440
4	29.46	0.440
5	19.58	0.440

6	25.46	0.440
7	26.037	0.440
8	27.638	0.440
9	26.076	0.440
10	29.191	0.440
Avg.	25.593	0.440
Std. Dev.	2.92	0.00

Test Object

Initial tests were done to identify a material that could be used as a test object, something that would vary capacitance. We decided upon using a vegetable based upon the idea that the dielectric constant and the capacitive behavior might be similar to that of human tissue. Carrots were chosen because degradation would be at a minimum. What follows are the results from experimentation done using plain carrots without any sort of surrounding medium (table 10).

Carrots (table 10)

TRIAL	COND (μSM)	CAPAC. (ηF)
1	6.86	6.26
2	6.52	6.80
3	6.20	6.53
4	5.81	12.70
5	6.56	8.08
6	3.56	4.37
7	3.55	4.61
8	4.53	6.96
9	4.58	6.36
10	4.47	6.16
11	3.47	4.98
12	4.51	6.28
13	6.17	8.93
14	6.50	9.27
15	6.53	9.39
16	6.59	9.35
Avg.	5.40	7.31
Std. Dev.	1.26	2.18

Consequentially, the experiments that took place involved placing a test object in the gelatin medium. The test objects used were carrots, Band-Aids, and plastic. Carrots were placed in the medium in two ways. First, to evenly distribute carrots throughout the medium, the carrots were grated and mixed into the medium so as to form a single layer (fig. 2). Results are in table 11.

Layer of grated carrots in gelatin (table 11)

TRIAL	COND (μSM)	CAPAC. (ηF)
1	1.29	0.20
2	1.49	0.15
3	1.66	0.60
4	1.32	0.43
5	1.61	0.13
6	1.68	0.28
7	1.80	0.51
8	1.96	0.20
9	1.61	0.27
10	1.66	0.30
11	1.72	0.23
12	2.05	1.08
13	2.22	0.58
14	2.02	0.89
15	1.53	0.37
16	2.48	0.72
17	2.53	0.80
18	1.45	0.31
19	2.10	1.11
Avg.	1.80	0.482
Std. Dev.	0.358	0.309

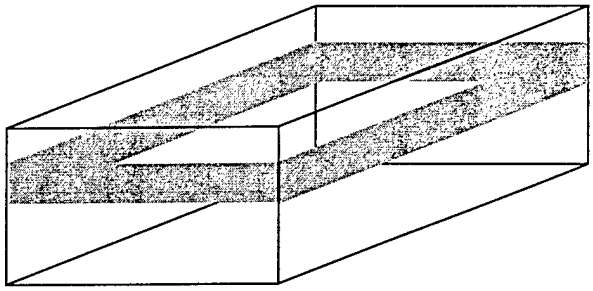


Fig. 2 -- a representation of the first phantom. In this case, the gray region is representative of the grated carrot layer, the rectangular box is the gelatin medium.

Next, whole carrots were inserted into the medium, in an upright fashion at different locations (fig. 3).

Carrots placed in clumps in Gelatin (table 12)

TRIAL	COND (μSM)	CAPAC. (ηF)
1	5.12	1.79
2	5.91	0.65
3	6.14	0.96
4	4.47	0.35
5	5.54	0.92
6	4.79	1.51
7	4.66	1.19
8	4.43	2.21
9	6.11	0.35
10	4.28	0.41
11	5.30	0.71
12	5.80	0.50
13	3.01	0.78

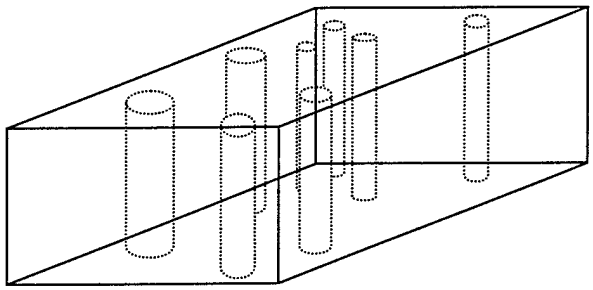


Fig. 3 – a representation of the second phantom. Again, the rectangular box is representative of the gelatin medium. The dotted cylinders represent the carrots placed upright in the medium.

14	3.09	0.35
15	3.79	1.56
16	3.52	0.32
17	4.52	0.69
18	3.44	0.24
Avg.	4.66	0.86
Std. Dev.	1.02	0.57

Other test objects were then used to see how much capacitance could be varied. One phantom was prepared using Band-Aids. Band-Aids were used under the assumption that cotton and plastic would have high dielectric constants that might be similar to that of biological tissue (fig. 4).

Band-Aids (table 13)

TRIAL	COND (μSM)	CAPAC. (ηF)
1	2.36	0.21
2	1.92	0.16
3	2.57	0.65
4	1.82	0.56
5	3.31	0.50
6	2.74	0.24
7	3.23	0.43
8	2.43	3.29
9	3.97	1.02
10	4.79	0.40
11	5.63	0.93
12	3.35	2.23
Avg.	3.18	0.89
Std. Dev.	1.15	0.94

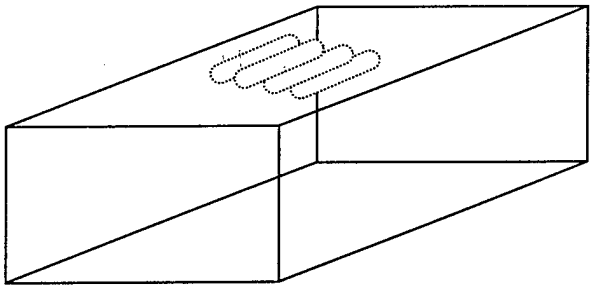


Fig. 4 -- a representation of the third phantom. The rectangular box represents the gelatin and the dotted lines outline the form of the Band-Aids that were used. There were 8 Band-Aids used, 4 pairs were placed on the surface of the gelatin.

Sheets of overhead transparency film were then inserted into the gelatin (fig. 5). Again, this was done because of the high dielectric constant of plastic. Unfortunately, capacitance did not vary at all upon using these sheets of plastic.

Plastic in Gelatin (table 14)

TRIAL	COND (μSM)	CAPAC. (ηF)
1	3.13	0.440
2	2.93	0.440
3	3.02	0.440
4	2.81	0.440
5	2.71	0.440
6	2.72	0.440
7	2.67	0.440

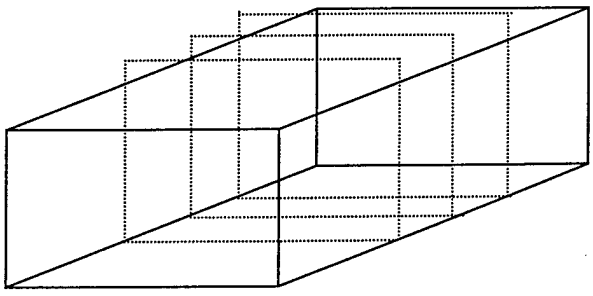


Fig. 5 – another phantom representation. The rectangular box is the gelatin and the dotted lines outline the three sheets of plastic that were inserted into the gelatin.

8	2.72	0.440
9	2.81	0.440
10	2.76	0.440
Avg.	2.83	0.440
Std. Dev.	0.15	0.00

Analysis of the data from the tool brought to light large inconsistencies -- namely, the large standard deviations that came about after multiple trials

Standard Deviations (table 15)

EXPERIMENT, DATE	STAND. DEV.	
	Cond. (μSm)	Capac. (ηF)
Right fingers, 06/30/99	0.930	0.76
Left fingers, 06/30/99	0.30	0.44
Right arm, 06/30/99	0.36	0.47
Left arm, 06/30/99	0.043	0.110
Plain gelatin,06/30/99	2.41	0.00
<0.2% gelatin, 06/30/99	0.15	0.00
0.2% gelatin, 06/30/99	2.92	0.00
Band-Aids, 06/30/99	1.15	0.94
Carrots, 07/11/99	1.26	2.18
Grated carrots in gelatin, 07/11/99	0.358	0.309
Vertical carrots in gelatin, 07/11/99	1.02	0.57

Such discrepancies indicated a need for improved understanding of the instrumentation in it of itself. An initial concern was with the calibration of the instrument. According to the patent, the instrument performs a self-calibration upon start up. Once assured of this fact, the reliability of the probe was investigated. A series of experiments were done in which resistors and capacitors

were touched to each of the 256 pads on the probe. These resistors and capacitors were used in the following way:

1. A resistor (1MΩ) was connected to the A/C source on one end (via an alligator clip) and the other end (also connected to an alligator clip) was touched to each pad on the probe. The use of the alligator clip proved to be an important factor in running these tests. It turned out that the amount of air the pad was in contact with affected the consistency of the measurements. By using an alligator clip, we were assured of the fact that most, if not the entire surface of the pad was in contact with the resistor. The results of the experiment are shown in fig. 6.

1.23	0.80	0.54	0.44	0.48 0.10	0.49 0.09	0.53 0.12	0.51 0.15	0.53 0.01	0.51 -0.09	0.50 -0.11	0.45 0.01	0.94 -0.03	0.88 -0.14	0.00 0.00	0.00 0.00
0.80	0.57	0.46	0.39	0.47 -0.10	0.51 0.10	0.46 -0.23	0.46 -0.13	0.30 0.06	0.28 -0.01	0.51 0.12	0.47 -0.15	1.06 -0.05	0.95 0.09	0.00 0.00	0.00 0.00
0.40	0.54	0.22	0.23	0.25 -0.05	0.27 -0.13	0.17 0.06	0.14 0.02	0.15 0.04	0.17 -0.04	0.23 -0.03	0.29 0.05	0.25 0.01	0.27 0.05	0.49 0.01	0.50 0.01
0.48	0.47	0.22	0.27	0.18 -0.01	0.15 -0.03	0.12 0.24	0.25 0.01	0.28 0.07	0.28 -0.06	0.25 -0.11	0.22 -0.05	0.19 0.02	0.27 0.04	0.51 0.04	0.48 0.01
0.53 0.09	0.48 -0.03	0.29 -0.06	0.26 0.10	0.25 -0.06	0.24 -0.06	0.17 -0.04	0.17 0.04	0.17 -0.03	0.15 -0.01	0.15 -0.04	0.17 -0.06	0.31 0.01	0.32 -0.04	0.49 0.05	0.47 0.10
0.49 0.02	0.40 0.10	0.17 0.11	0.27 0.05	0.26 -0.07	0.20 0.02	0.15 0.10	0.17 0.04	0.18 0.02	0.16 -0.06	0.17 -0.01	0.14 0.09	0.28 0.05	0.26 0.16	0.37 -0.16	0.52 0.23
0.43 0.20	0.42 -0.13	0.24 0.12	0.26 0.01	0.15 0.02	0.16 -0.03	0.11 -0.04	0.11 -0.03	0.10 -0.05	0.10 0.03	0.15 0.05	0.15 0.00	0.10 0.05	0.22 -0.05	0.38 -0.09	0.46 -0.29
0.43 -0.22	0.42 -0.12	0.27 -0.01	0.25 0.03	0.18 -0.02	0.19 0.03	0.10 0.01	0.11 -0.00	0.12 -0.05	0.10 0.05	0.15 -0.03	0.18 -0.01	0.15 0.04	0.17 -0.05	0.48 -0.20	0.53 0.03
0.48 0.16	0.59 -0.16	0.14 -0.01	0.14 0.05	0.11 -0.02	0.12 0.01	0.10 0.01	0.10 0.00	0.11 0.02	0.10 -0.01	0.11 -0.01	0.10 0.00	0.14 0.04	0.12 0.05	0.36 0.02	0.47 -0.15
0.47 0.16	0.45 -0.06	0.17 0.04	0.17 0.02	0.19 0.05	0.17 -0.01	0.11 -0.05	0.11 0.03	0.12 0.00	0.10 0.01	0.11 0.03	0.10 0.00	0.15 -0.03	0.11 0.02	0.40 0.18	0.36 -0.02
0.47 -0.04	0.44 -0.06	0.27 -0.05	0.25 -0.01	0.28 -0.01	0.26 0.07	0.18 0.01	0.13 -0.03	0.18 -0.03	0.18 -0.04	0.20 0.01	0.22 -0.02	0.24 0.00	0.21 0.06	0.56 0.14	0.34 0.10
0.55 -0.10	0.44 -0.01	0.26 -0.05	0.23 -0.00	0.24 0.18	0.23 0.04	0.18 0.00	0.16 -0.05	0.16 -0.06	0.16 -0.04	0.28 -0.04	0.21 0.05	0.26 -0.03	0.24 -0.02	0.47 0.04	0.34 -0.13
0.59 -0.25	0.58 -0.01	0.25 0.14	0.17 -0.03	0.22 -0.03	0.25 0.10	0.29 -0.07	0.25 -0.09	0.22 -0.03	0.25 0.10	0.29 -0.07	0.25 -0.09	0.16 0.00	0.16 0.01	0.17 0.05	0.17 0.05
0.41 0.03	0.56 -0.11	0.28 0.10	0.20 0.00	0.23 -0.05	0.19 -0.03	0.27 -0.01	0.30 -0.02	0.23 -0.05	0.19 -0.03	0.27 -0.01	0.30 -0.02	0.17 0.00	0.16 0.01	0.17 -0.03	0.16 0.03
1.18 -0.26	0.84 -0.47	0.53 0.33	0.55 0.29	0.48 -0.22	0.50 -0.23	0.44 -0.24	0.56 0.18	0.48 -0.22	0.50 -0.23	0.44 -0.24	0.56 0.18	0.51 0.09	0.51 0.03	0.49 -0.03	0.43 0.05
1.03 -0.52	1.16 -0.26	0.58 0.03	0.59 -0.12	0.46 0.11	0.53 0.18	0.58 0.16	0.57 -0.06	0.46 0.11	0.53 0.18	0.58 0.16	0.57 -0.06	0.48 0.03	0.50 0.04	0.49 -0.01	0.49 0.05

Fig. 6 -- In each box, the top value is conductivity (in μSm) and the bottom is capacitance (in ηF). Capacitance should be at or above zero in all cases. For a graphical analysis of the same data, please see the appendix.

2. Next, a resistor (1MΩ) and a capacitor (0.001 μF) were connected in parallel. One side of the circuit was connected to the A/C source (via an alligator clip). The other side was connected to an alligator clip that the probe was touched with. Results are shown in fig. 7.

0.85 1.18	1.41 1.19	0.50 0.08	0.69 0.90	0.41 0.67	0.50 0.74	0.54 0.64	0.55 0.52	2.59 1.29	1.80 1.45	0.00 0.00	1.00 1.16	0.94 2.2	1.28 1.56	0.00 0.00	0.00 0.00
0.98 0.13	0.98 1.13	0.61 .81	0.54 0.39	0.50 0.42	0.50 0.48	0.46 0.72	0.46 0.54	0.37 1.64	0.54 -0.63	0.76 0.10	0.13 1.17	0.96 0.74	0.98 0.79	0.00 0.00	0.00 0.00
0.41 0.47	0.42 0.77	0.32 0.36	0.24 0.39	0.24 0.26	0.21 0.32	0.23 0.29	0.3 0.26	0.16 0.27	0.42 0.83	-0.02 0.54	0.00 0.00	0.25 0.14	0.21 0.11	0.54 0.37	0.40 0.21
0.49 0.64	0.43 0.28	0.25 0.41	0.25 0.17	0.21 0.22	0.47 0.30	0.42 0.27	0.24 0.35	0.26 0.46	0.19 -0.21	0.00 0.00	0.34 1.14	0.27 0.28	0.25 0.44	0.45 0.40	0.54 0.26
0.53 0.45	0.54 0.84	0.23 0.31	0.27 0.41	0.25 0.16	0.22 0.19	0.56 0.45	0.10 0.53	0.27 0.26	0.25 0.15	0.23 0.24	0.22 0.23	0.27 0.06	0.22 0.15	0.82 1.02	0.43 0.59
0.48 0.04	0.54 0.55	0.24 0.27	0.22 0.24	0.24 0.30	0.21 0.18	0.55 0.36	0.57 0.57	0.17 0.20	0.15 0.22	0.21 0.27	0.28 0.23	0.27 0.38	0.28 0.26	0.44 0.65	0.51 0.38
1.12 1.15	0.77 1.05	0.23 0.20	0.50 0.44	0.46 0.30	0.22 0.23	0.23 0.26	0.27 0.20	0.89 0.79	0.19 0.30	0.27 0.20	0.18 0.26	0.16 0.22	0.19 0.11	0.33 0.33	0.37 0.28
0.05 0.33	0.30 0.37	0.30 0.13	0.28 0.22	0.29 0.35	0.19 0.23	0.30 0.36	0.25 0.30	0.26 0.24	0.18 0.19	0.24 0.28	0.19 0.18	0.19 0.20	0.23 0.24	1.04 0.68	0.32 0.33
0.51 0.62	0.36 0.39	0.10 0.41	0.17 0.23	0.23 0.36	0.22 0.29	0.31 0.24	0.20 0.22	0.51 0.38	0.48 0.48	0.27 0.20	0.25 0.19	0.19 0.20	0.25 0.18	0.83 0.93	0.40 0.51
0.34 0.46	0.35 0.39	0.44 0.29	0.42 0.32	0.20 0.22	0.16 0.22	0.23 0.31	0.23 0.13	0.25 0.27	0.25 0.15	0.21 0.28	0.23 0.28	0.24 0.30	0.23 0.38	0.33 0.29	0.59 0.66
0.40 0.33	0. 29 0.22	0.29 0.15	0.18 0.23	0.15 0.14	0.18 0.20	0.16 0.28	0.16 0.12	0.25 0.29	0.23 0.34	0.23 0.29	0.21 0.23	0.23 0.33	0.24 0.25	0.53 0.46	0.53 0.58
0.38 0.33	0.63 0.35	0.16 0.21	0.25 0.13	0.27 0.29	0.24 0.24	0.17 0.18	0.15 0.19	0.26 0.31	0.21 0.27	0.27 0.24	0.22 0.22	0.23 0.22	0.21 0.31	0.41 0.80	0.42 0.58
0.48 0.45	0.46 0.31	0.23 0.30	0.21 0.31	0.23 0.22	0.28 0.23	0.52 0.28	0.44 0.37	0.15 0.21	0.16 0.21	0.26 0.33	0.22 0.21	0.24 0.25	0.25 0.24	0.25 0.28	0.52 0.42
0.51 0.68	0.49 0.48	0.23 0.27	0.22 0.29	0.25 0.34	0.26 0.23	0.50 0.43	0.47 0.34	0.14 0.23	0.19 0.13	0.22 0.23	0.22 0.30	0.27 0.19	0.24 0.29	0.48 0.56	0.47 0.45
1.01 1.00	0.90 0.80	0.53 0.45	0.43 0.52	0.49 0.45	0.47 0.41	1.01 1.16	1.10 1.10	0.53 0.36	0.45 0.38	0.51 0.29	0.49 0.63	0.26 0.30	0.47 0.49	0.49 0.39	0.53 0.48
1.04 1.07	0.93 1.17	0.48 0.48	0.50 0.71	0.52 0.46	0.54 0.47	0.92 0.94	0.97 0.98	0.53 0.35	0.52 0.34	0.52 0.59	0.45 0.29	0.59 0.50	0.45 0.41	0.60 0.49	0.52 0.51

Fig. 7 – This is a map similar to the one in fig 6. Again, to see a graphical analysis, please see appendix.

From these experiments, we obtained results that once again trouble us. In both experiments, our expectations were twofold:

1. There was an expectation that from pad to pad, there would be a slight discrepancy, but no bigger than a 10% difference such a small difference was not achieved in these experiments. We did expect, on the other hand, a greater discrepancy for the pads on the periphery of the probe. According to the patent, since the probe doesn't cover the entire region of interest, the edge of the impedance image will be slightly distorted. In theory, the probe is at a ground potential. When it is placed on the patient over the area of interest, the electric field that is produced from the alternating current the patient is exposed to will be perpendicular to the surface of the probe. If there are no variations of impedance directly below the probe, each element will take a measurement of integrated impedance. In actuality, the probe doesn't necessarily cover the areas of interest completely. The areas beyond the boundary of the probe are not at ground potential. The field lines bend at the boundary of the probe and bring about distortion in the impedance images. This distortion is controlled through the use of a "guard ring". The guard ring acts to straighten the field lines at the edge of the probe by ignoring the measurements taken by the elements at or near the edge.[ix] As such, one would expect a greater consistency in measurement from pad to pad. This was not the case in our measurements.
2. Our second expectation was to achieve a conductivity value of 1 μSm when using a 1MΩ resistor. A multi-meter was used to ensure that the expected values were valid expectations. From the data, one can see that this value was not obtained. The values were, on the other hand, grouped around one number in most cases. Effectively, this told us that we could not rely on the absolute values of the machine, but that there might be a manner in which a correlation could be made between expected and actual values.

Discussion

Although the prospect of eventually using TransScan as an adjunctive means of detection of breast cancer is good, there are items of concern that should be addressed.

One cause for concern is the lack of a phantom to mimic breast tissue of differing compositions – that is of differing degrees of fatty tissues. The information garnered from these experiments will lay the basis for future investigation. The standard measurements of human tissues that were taken (conductivity is in the range 1-4 μSm and capacitance is in the range 2-5 ηF) can be used to find the proper medium and test objects which meet our criteria. What was done through these experiments was a step in the right direction. Eventually, it is hoped that we will be able to place items such as human tissues (both cancerous and not) within the phantom and be able to detect it. The phantom will be varied to reflect fattier or more glandular breast tissue.

Further cause for concern has to do with the probe itself. From test to test, there were marked inconsistencies that were further confirmed by tests done on the specific elements of the probe. It was shown that measurements taken at the center of the probe were the only reliable ones. Also, there will most probably be a graded difference in the appearance of the cancer from center to edge. These are causes for concern clinically. It means that in order to ensure reliable results one must place the probe directly upon the area of interest being sure the probe is centered upon the area of interest.

Additionally, it was found that the absolute values obtained from TransScan could not be relied upon. No correlation could be made between the TransScan numbers and the numbers that should have been found. Clinically, this has an impact, too. It means that the instrument can only be used accurately after has had much experience using the instrument on patients. This

would imply the need for general knowledge of the differences in conductivity and capacitance that one should expect from cancerous tissues.

Currently, our version of TransScan is being upgraded. Once accomplished, similar experiments will be done on the new probes to ensure reliability and consistency. Furthermore, as our phantom continues to be developed, it will be used to ensure diagnostic accuracy.

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[i] Statistics from the American Cancer Society home page (www.cancer.org)
[ii] Statistics from the National Cancer Institute home page (cancernet.nci.nih.gov)
[iii] not sure
[iv] Principles of Bioelectrical Impedance analysis by Rudolph J. Liedtke
[v] Suroweic et al.
[vi] Jossinet
[vii] B Blad and B Baldetorp
[viii] US patent no. 5,810,742 inventor: Pearlman, Andrew L
[ix] patent

August 21, 2001
Dr. Kathryn Moore
USAMRMC
ATTN: MCMR-PLF/Ms. Kathryn Moore
504 Scott Street
Fort Detrick, MD 21702-5012

Re: Revision of research protocol. DAMD17-00-1-0260: Electrical Impedance Imaging of the Breast: Correlation with MRI, US, Sestamibi, and Histology with Measures of Cell Proliferation and Vascular Density

Dear Dr. Moore:

Based on my own research and newly published information, I have revised the protocol for this project and am requesting approval of the new protocol.

The basic purpose of this grant was and is to derive data to improve the sensitivity and specificity of electrical impedance imaging (EII) by comparing it to imaging features of from ultrasound, MRI and Sestamibi and, when there is a biopsy performed, to correlate the findings with special histology analyses. Based on the originally available data, we thought that the main problem would be to distinguish those features that separated positive and negative EII findings in both benign and cancer cases.

In our work with this FDA approved system in both patients and research volunteers from other protocols, we now consider that the direction of this project for the next year or perhaps more should be to focus on what is causing the many false positive EII results in what appears to be completely normal breast tissue. There are sometimes as many as five such EII spots in each breast. The next step is to work to determine the characteristics of EII positive findings when there appear to be no lesions present.

This approach will involve a more intensive evaluation of each volunteer (because we need to evaluated as many as 10 sites in both breasts, rather than just one) and therefore fewer volunteers overall for this phase of the research.

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2115 Wisconsin Avenue, Northwest, Suite 603
Washington, DC 20007

We have found that ultrasound is the modality most likely to provide us with the anatomic and vascular flow information needed for this part of the study and thus will emphasize correlation with ultrasound. It is also much easier to correlate the position found with ultrasound to that of EII, than with MRI or mammography. At this time, imaging with 99mTcSestamibi does not appear to be sensitive enough to provide useful information so we will not be using it for this study. Some patients will have MRI correlation as well. Our interest in the MRI correlation is now extended to the MRI visible "incidental enhancing lesions" to determine any relationship to the EII active lesions.

I believe that this revised protocol decreases the risks to the volunteers by eliminating parts of the study that no longer appear necessary.

Incidentally, the company has chosen to change the name for the imaging to Electrical Impedance Scanning (EIS), so I have used the new name in the new protocol.

It remains clear that EII detects accurately many breast cancers, but it is not yet good enough for routine clinical use. I believe that the approach we have described in the protocol will provide data that can be used to improve the system. A recent article (Malich et al. EIS for classifying suspicious breast lesions. Eur Radiol 10, 1555-61. 2000) supports the value of EIS, but also found problems with the many false positive detections. I have enclosed a copy.

I trust that your review will approve the change in focus and the modified protocols. EII imaging is proving to be more complex than I anticipated based on the data available at the time the proposal was submitted to the US Army. It will require a different approach for its solution.

Sincerely yours,

Matthew Freedman, MD, MBA
Principal Investigator
Associate Professor of Radiology

Voice: 202-784-3417, Fax: 202-784-3479, email: freedman@isis.imac.georgetown.edu.

Georgetown University Institutional Review Board Application (Protocol) for Biomedical IRB Review (AB-1)

Section One: Application Information

Principal Investigator	Matthew Freedman, MD, MBA
Department	Radiology/Lombardi Cancer Center
Title	Associate Professor of Radiology
Responsible Participant (member of faculty or official or administrative unit)	Matthew Freedman, MD, MBA

Title of Project	**Purpose of Project (one or two sentences)**
Electrical impedance imaging of the breast: Correlation with MRI, US, Sestamibi and histology with measures of cell proliferation and vascular density.	To determine basis for true positive and false positive findings on electrical impedance imaging by correlation with US and histology, primarily, and secondarily with MRI.

Consultants or co-investigators, if any	**Department or Institution**
Erini Makariou, MD	Radiology
Baljit Singh, MD	Lombardi Cancer Center

Estimated duration of total project	3 years
Estimated total number of subjects (including control subjects)	100
Age range of subjects	Age 35 and older
Sex of subjects	Female
Where will study be conducted?	MedStar Georgetown Hospital and Georgetown University
Source of subjects	Ourisman Breast Health Center, MedStar Georgetown Hospital

Grant Support for Project (if any) (Attach 2 copies)	**Commercial Support (if any) for Project**
US Army Breast Cancer Program	

Section Two: Additional Georgetown University Regulatory Information

1. Does this project involve the use of biohazardous materials, recombinant DNA and/or gene therapy?
   - ☐ Yes. If so, Institutional Biosafety Committee (IBC) approval must be obtained. Contact 202-687-4712 for assistance.
   - ☐ No.

1. Has the Institutional Biosafety Committee approved the protocol?

☐ **Approved**	**Date Approved:**
☐ **Application Pending**	**Date Submitted:**

1. Does this project include the use of radioisotopes and/or radiation-producing devices regardless of whether the use is incidental to the project?
   - ☐ Yes. If so, all protocols must be submitted to the GUH RSC along with a completed RSC-4 or RSC-5 form. The forms require information on the use of radioisotopes and radiation-producing devices and must include dose calculations. Call 202-687-4712 to obtain forms or if additional information is required.
   - ☐ No.

1. Has the Radiation Safety Committee approved the protocol?

☐ **Approved**	**Date Approved:**
☐ **Application Pending**	**Date Submitted:**

1. Does this project involve the use of fetal tissue?
   - ☐ Yes
   - ☐ No

1. Is there a current Conflict of Interest form for each investigator on file at the Office of Regulatory Affairs?

Not applicable. Under University Rules as I understand them, no statement needs to be filed if no conflict exists.

- ☐ Yes
- ☐ No. If not, please fill out the form (which can be found in the Georgetown University Faculty Handbook, forward the original to the Office of Regulatory Affairs, and attach a copy to this application).

Section Three: Information for Protocol Review
Please answer each specific question and use additional sheets as needed. A response of "See attached protocol or grant application" is not sufficient.

1. Provide a brief historical background of the project with reference to the investigator's personal experience and to pertinent medical literature. Use additional sheets as needed.

Electrical impedance scanning (EIS) of the breast is a new method for the evaluation of equivocal lesions in the breast found by mammography or clinical breast exam that remain equivocal following evaluation by diagnostic mammography and by ultrasound in those cases where ultrasound is indicated. It is FDA approved (June 16, 1999) for the adjunctive assessment of these equivocal lesions. The method currently is described by four different names: Electrical impedance scanning (EIS in this document), Electrical impedance spectroscopy, Electrical impedance imaging (EII), and T-Scan (from the manufacturers name for the system).

Based on the available data and work we have performed in phantoms and patients, the PI would like to investigate the system in more detail to better determine the features that result in true positives, false negatives, and false positives. Our clinical experience and research performed under Georgetown IRB Protocol 96-22 has shown that the system produces a large number of false positive detections that, we think, make it inappropriate for current clinical use. While it remains FDA approved and has undergone two FDA approved updates, we wish to continue to use this as an experimental, rather than a clinical device.

The T-Scan system is approved for use in determining the likelihood of malignancy in women whose mammograms have been classified using the American College of Radiology's standard Breast Imaging Reporting and Data System (BIRADS). FDA approval has been given for the investigation of women classified as BIRADS 3 and 4. BIRADS 3 are those lesions that are probably benign, but for which short term follow-up is recommended. BIRADS 4 are those lesions where malignancy cannot be excluded and for which biopsy should be considered. BIRADS 4 lesions are expected to have a chance of malignancy of about 10%. For BIRADS 3 lesions, the chance of malignancy is expected to be 1-2%.

Electrical impedance imaging of the breast has been under development for more than 20 years. Each tissue in the body has a specific range of electrical characteristics that can be used to define it. (1-7) If two tissues next to each other have different characteristics, then it is possible to identify that these two tissues are different and to create an image resulting from the tissue differences.

Tissues differ in three main electrical features. First there is a cell membrane potential that differs between the cells in normal, fatty, and cancerous tissue. This can be detected by placing an electrode within the tissue and measuring the DC current that results. Second, there is the conduction of electrons through tissue. The electrical resistance of tissue to the conduction of electrons appears to depend on cellular density, vascularity and the amount of extracellular fluid. Third, cell walls and intercellular tight boundaries function as capacitors. Capacitance appears to be related to the density of cellular packing. If one applies an alternating current to the body, then one can measure the combination of resistance and capacitance. This combination of resistance and capacitance is called impedance. In the breast, fatty tissue, glandular tissue, and breast cancer of various types (ductal carcinoma in situ, invasive ductal carcinoma and lobular carcinoma) should differ in their impedance properties as this has been shown in vitro.

Although these electrical properties of tissue have been known for more than 30 years, converting laboratory data done on tissue samples into clinically useful systems for breast cancer detection has been quite slow. It has become practical today only because of major improvements in electronics and computer technology as well as several important conceptual breakthroughs in software design. (8-10) The first commercial machine for electrical impedance imaging of breast cancer received FDA approval June 16, 1999 (11-13). We have had this approved system in our laboratory since the Summer of 1999 for testing and have received updated equipment as released by the manufacturer and FDA.

The investigators for this project are convinced that a consistent scientific approach in the evaluation of this system will increase its benefit to women for detecting breast cancer by helping us understand the cause of the large number of false positive findings. The available data, and our own investigations of the machine, convinced us that this method can indeed detect

breast cancer that cannot be detected by mammography in those women who have increased breast density. The manufacturer, TransScan, has agreed to supply the machine, all upgrades and maintenance to us for three years at no cost to pursue our research.

Previous work demonstrating the benefit from Electrical Impedance Imaging of the Breast

In the process of obtaining FDA approval, the manufacturer acquired clinical data in several different clinical trials of which one is described. (13) From 1995 through early 1997: the company obtained data from seven centers comparing the accuracy of mammography compared to mammography combined with EIS. 745 patients (1490 breasts, of which 504 underwent biopsy) were examined separately and blindly by mammography and by EIS. Radiologists reinterpreted EIS surveys of the whole breast and mammographic 2-view images of all 1490 breasts separately and blindly, and scored them using a 5-point level of suspicion (LOS) scale: LOS 3,4, or 5 was considered positive. A combined adjunctive score in the area of the mammographic finding was then calculated. If the electrical impedance score (EIS) was positive, the LOS score was increased by 1 unit. If the EIS was negative, the LOS score was decreased by 1 unit. Diagnostic accuracy was determined based on pathology findings.

Results: There were 325 benign and 179 malignant biopsies. Diagnostic accuracy for the EIS with mammography Vs. mammographic alone findings (the EIS with mammography values are given first):

For all cases: Sensitivity 86% Vs. 82% ($p = .10$), specificity 51% Vs. 39% ($p < 0.0003$),

- **For women under 50 years:** Sensitivity 85% Vs. 68% ($p = 0.02$), specificity 53% Vs. 41% ($p = 0.013$).
- **For palpable lesions:** Sensitivity 88% Vs. 81% ($p=0.18$), Specificity 50% Vs. 44% (n.s.= not statistically significant).
- **For nonpalpable lesions:** Sensitivity 84% Vs. 78% (n.s.), specificity 51% Vs. 41% ($p = 0.025$).

These results strongly support the usefulness of EIS in women under the age of 50 in whom the sensitivity of mammography was 68% and that of the combination of mammography and EIS was 85% ($p = 0.02$). The detection of early breast cancer in women under the age of 50 is a major area of clinical concern. Because of the lower sensitivity of mammography in these women and the lower frequency of disease, the cost of screening with mammography is higher. Because it is difficult to distinguish benign processes and cancer in the radiodense breast more benign biopsies are performed in younger women. EIS may represent an important breakthrough in detecting breast cancer in younger women.

Report of the *Breast Cancer Progress Review Group: Charting the Course: Priorities for Breast Cancer Research*.

In 1998, the National Cancer Institute released an intensive review of opportunities for new advances in the effort to control breast cancer (14). This extensive report proposed future directions for breast cancer research. In Chapter 5: Detection, Diagnosis and Prognosis. The committee had several recommendations. They included: "*Detection-Related Questions and Opportunities*: A. Determine the potential of newer imaging technologies (e.g., ...electrical impedance imaging....) to detect and diagnose clinical significant breast disease better than is currently done by physical examination and conventional mammography. . . Foster more basic research into the most novel imaging technologies (e.g., ...electrical impedance imaging....)." EIS is recognized by this NCI committee as a new and promising modality for breast imaging for

which further research is recommended.

Previous work in EIS at Georgetown

In July, 1998, the PI of this project identified EIS of the breast as an important future method for breast cancer detection. Approaches to TransScan were initially unsuccessful, but eventually a system was placed in the Ourisman Breast Health Center in June, 1999. During July and August, 1999, extensive laboratory tests were made of the system. A 33 page report was prepared for internal use and also sent to the company.

We realized that the EIS system could detect cancer, but that it still failed to detect 15% of breast cancers. One question we want to address was what the difference was between the cancers detected and those not detected and how could this information help improve the EIS methods.

Engineering tests were implemented.

The engineering work performed involved two different efforts. First, we worked to develop a group of tissue equivalent phantoms so that we could better control our experiments. We were able to create phantoms with characteristics that simulated the differences between the fatty breast and two degrees of glandular breast. We produced simulated breast cancers in the phantoms. We also developed methods for testing the resolution of the system. The second effort was to develop methods to test the calibration of each sensor component of the detector probe that is applied to the breast so that we could be certain that measurements made with the system would be reproducible. The company currently provides no tissue equivalent phantoms and no method for testing the accuracy of the sensor efforts.

Our eventual goal is to develop methods to compare the following characteristics of breast lesions on EIS and US: Lesion size, lesion depth, thickness of fat layer between lesion and detector probe, thickness of glandular tissue between lesion and detector probe, and lesion vascularity as defined by Doppler ultrasound. Because fat is a relative non-conductor it could both limit the transfer of the electrical signal to the tissue and limit its detection at the skin surface. Glandular tissue is a moderate conductor of electricity and should improve the detection at the skin surface. Most of the electrical signal reaching breast cancer is thought to come through its vascular supply. Thus the measurement of vascularity by Doppler ultrasound should provide useful information on the biology of EIS detection. These ultrasound features will be combined with information from the mammogram and lesion histopathology to provide better understanding of EIS and its role in early breast cancer detection—why it succeeds and why, in some cases, it fails to detect the cancer. In addition, high resolution ultrasound is currently a competing method for assessment of breast masses to determine if they are malignant and one manufacturer (ATL, Inc.) received FDA approval for this use. As our work continues, we should be able to determine the relative accuracy of ultrasound and EIS for better defining the benign or malignant characteristics of breast lesions. The EIS company did not compare ultrasound and EIS in their FDA study.

In 2001, Malich (15) reported an initial study combining EIS with US and MRI. In their study of 100 patients with suspect lesions seen my mammography, 50 of 62 malignant lesions were correctly identified by EIS (81% sensitivity). 24 of 38 benign lesions were correctly identified by EIS (63% specificity). Kappa was 0.82 between MRI and EIS and 0.62 between US and EIS. They report that artifacts currently result in the high false positive rate of EIS. Our experience is that the false positives are sufficiently frequent so as to interfere with our confidence in the accuracy of the system. It is for this reason that we will be shifting our focus to a more careful analysis of the false positives produced by the system.

The EIS Device: T-Scan 2000

The T-Scan 2000 (TransScan Ltd., Migdal Ha'Emek, Israel) non-invasively maps the electrical impedance of the breast tissue at various frequencies, in real-time, using a minuscule electrical signal applied via an electrode on the body. A voltage applied at the patient's hand results in a minuscule current flowing to the breast, where a probe with an array of electrical sensors, measures the local current density and phase relative to the applied signal. In the absence of a tumor, current lines are relatively homogeneous across the breast surface, reflecting the moderate range of impedance variance among the various normal breast tissues. The presence of a tumor, which is a low impedance lesion, causes a local distortion in the electrical field and hence in the current distribution, which is detected at the skin surface as a change in local current density and phase. These changes are detected on the breast skin by the hand-held "scan probe", which houses the 35 x 35 mm (small probe) or 65 x 65 mm (large probe) square array of sensors. At each position on the breast the scan probe produces non-invasively and in real-time, a grayscale map of the local distribution of tissue electrical impedance at various frequencies.

In the T-Scan image, the nipple is the only normal object that appears bright white. The remaining normal breast tissue is seen to have varying shades of gray. If a carcinoma is present, it stands out as a bright, white object in the image, against the relatively homogeneous gray background. Malignant tumors of sizes ranging from 1 mm to over 5 cm in all parts of the breast have been detected by T-Scan, as well as atypical hyperplasia, which often exhibits a low impedance as well.

This technology carries no known risk, is comfortable to the patient, and is less expensive than mammography.

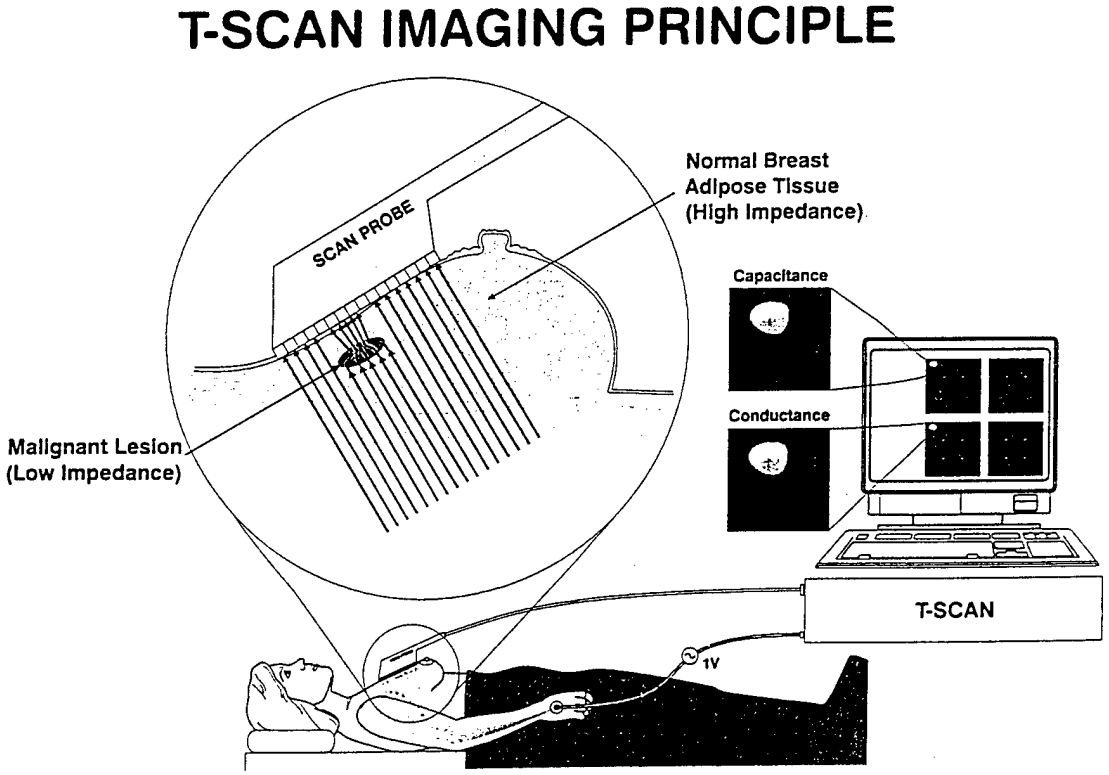

Figure 1 T-Scan imaging principle

1. The plan of study. State the hypothesis or research question you intend to answer. Describe the research design and procedures (including standard procedures) to be used in the research. Specifically identify any experimental procedures. Provide statistical justification for the number of subjects to be studied and the degree of change expected. Describe any special equipment or unusual procedures to be used for this research project. Use additional sheets as needed.

Primary Objective: Evaluate the adjunctive impact of Electrical Impedance Scanning (EIS) upon the diagnostic accuracy of mammography in equivocal cases that may be benign or cancer.

Secondary Objective: To determine the imaging parameters of lesions identified by T-Scan that are true positives, false positives and false negative recordings by correlation with other imaging methods and with pathology in those cases in which biopsy is performed.

New Secondary Objective: To map the structure of EIS false positive detections by correlation with ultrasound and Doppler ultrasound, and in some cases with MRI. In a limited number of women to study the correlation of these findings with the menstrual cycle.

Hypotheses:

1. Use of Electrical Impedance Scanning (EIS) as adjunct to mammography in patients with equivocal findings increases the specificity and maintains or increases the sensitivity compared to mammography alone. The frequency of false positive findings decreases the systems clinical usefulness.
2. Careful analysis of false positive EIS findings will enhance understanding of the characteristics of these false positive lesions and will enhance the ability to enhance specificity of the system.

Experimental Design:

Original Patient Population:

1. Patients with abnormal findings at screening mammography or clinical examination who have been advised to have breast biopsy will asked to participate in this project. Most of these women will have clinically indicated ultrasound examinations. A smaller number will have breast MRI examinations as part of their clinical care. The results of these clinically indicated studies will be incorporated into the analysis for this research.

Additional Patient Populations

2. Patients with apparently normal breasts based on mammography, but with factors of high risk for the future development of breast cancer.
3. We will be submitting addenda to other breast imaging protocols to incorporate EIS studies in other populations and will refer to this protocol in those submissions.

4. Exclusion Criteria

Subjects will be excluded from the study who:

State that they are pregnant or might be pregnant when asked

Have actively powered implanted devices (e.g. pacemakers) (exclusion for EIS and MRI)

Are undergoing chemotherapy or radiation therapy for any cancer

Performing the T-Scan 2000 exam

Personnel: Each operator of the T-Scan device will be an employee of MedStar Georgetown University Medical Center or Georgetown University and have an RN, MD, RDMS or RT(R) degree or certification. Each will have completed appropriate training in the use of the T-Scan device and in the interpretation of T-Scan images.

The first time the T-Scan is used on a given day, the system automatically tests and calibrates its functions and remains calibrated throughout the day or until next power off/on. The T-Scan system is usually located at the head of the examination table, on which the patient nominally lies supine. The position of the patient during the examination is similar to that during an ultrasound examination. The patient lies on her back with the arm ipsilateral to the breast being examined, extended above her head. The purpose of this position is to flatten the breast as much as possible against the thorax, allowing the scan probe to be as close as possible to the suspicious lesion, and to record the nipple in standard orientation. We believe that this position may contribute to the frequency of false positive detections and will try alternative position including sitting and lateral decubitus positions as well.

The patient holds the source electrode in the hand contralateral to the breast being examined. The examiner applies ultrasound gel to the sensor array on the handheld probe and sprays a biocompatible conductive spray to the area of the lesion on the breast. The probe is gently pressed on the breast for the approximately 3-4 seconds needed to record both capacitance and conductivity in real time at each of a pre-determined list of frequencies.

Examinations are performed using the Spot View Mode of the T-Scan 2000, in which the examiner notes the position of the probe on an anatomical map of the breasts presented together with the images. The Spot View Mode allows recording of up to five sectors. The examination sequence is first record sector 1 at the site of the lesion in standard resolution (8 x 8), then repeat the recording in high resolution (16 x 16) in sector 2, then record the ipsilateral nipple in sector 3 and the contralateral nipple in sector 4. If an additional sector is indicated, it can be recorded in sector 5.

Research Design:

Women having diagnostic evaluation of the breast for suspect or definite breast lesions will be approached by a member of the research team and asked if they are willing to participate. Each woman will have the procedure explained to them by the Research Associate or other member of

the research team. Should they show interest in participating, they will be provided with the written consent form. If they agree to participate, the T-Scan and US will be performed within the Radiology Department at MedStar Georgetown Hospital.

T-Scan will be performed of the index lesion and with the patient in the same position, a directed ultrasound examination of the same site will be performed. At a minimum, sagital and transverse images will be obtained as well as Doppler images to document lesion vascularity. Once the index lesion has been evaluated, the breast will be surveyed with the T-Scan device. If there are other T-Scan positive foci, each (up to a maximum of five) will be evaluated with ultrasound. The effects of T-Scan positivity will be studied to see the effects of changes in patient position and in changes that occur when the breast is displaced to overlie different portions of the chest wall. In some cases the opposite breast will also be studied. Files will be kept of the corresponding images for T-Scan and US for each identified location. Each case will be recorded in a database recording lesion size, vascularity, depth, thickness of intervening fat and other features.

In up to 10 premenopausal women with positive T-Scan findings, we will request that they return for 4 to 8 weekly examinations so that the effect of the menstrual cycle on positive findings can be evaluated. This small group of volunteers will be paid $25 per visit for participating.

In women undergoing biopsy, the tissue will have special staining for assessment of breast cellular density and lesion vascularity. In cases of breast cancer, these special histology measurements may be clinically indicated as part of the patient's normal care. We will also be studying the benign lesions that undergo biopsy. In these cases, and in those breast cancer cases where the special studies are not clinically indicated, the grant will cover the costs of the additional pathology analysis.

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1. Indicate what you consider to be the risks to subjects and indicate the precautions to be taken to minimize or eliminate these risks. Justify the need for a placebo control group if one is included in this study. Where appropriate, describe the data monitoring procedures that will be employed to ensure the safety of subjects. Use additional sheets as needed.

We believe that this protocol entails minimal risk for the subjects. There are two types of risks we have considered: machine based risks and misdiagnosis risks:

Machine based risks:

More than 20,000 breast examinations have been performed with the TransScan TS 2000 and predecessor devices without complications. The system is electrically isolated and meets all US and European electrical safety standards. An occasional women is aware of a slight tingling sensation, usually in the hand that holds the electrode. The volunteers have told us that this is not uncomfortable.

Misdiagnosis risks:

T-Scan is a diagnostic method for breast cancer and is FDA approved as a diagnostic tool. The system can detect breast cancer. It is not FDA approved as a detection tool. In most women it also provides false positive readings (ie detections in the absence of cancer and in some cases without identified cause). Because of the false positives, we believe that no action should be taken on an unconfirmed T-Scan abnormality. The goal of the project is to try to understand the nature of these false positives. For this reason, we will perform ultrasound for up to five false positive locations per woman. In some cases ultrasound may detect a lesion that was not seen on mammography. This focal lesion may have characteristics of possible cancer warranting biopsy. For these women, one would expect only 20-25% will actually have cancer. Thus there are two risks: First, that a T-Scan identified cancer will not be identified by ultrasound or mammography

and that biopsy will not be performed. T-Scan is however not FDA approved for this activity. Second, that an ultrasound exam prompted by the T-Scan will find a lesion appropriate for biopsy based on ultrasound criteria, but that this biopsy will show only benign findings.

The TransScan System is a new system that is similar to breast ultrasound, but will be unfamiliar to patients. It is FDA approved. When used within this research project we will use the following procedure: (1) When used in accord with its FDA approval indications for use, the information will be made available for clinical use and will be incorporated into the clinical report as appropriate. (2) When the information is made available for clinical use, we will depart from the FDA approved uses by advising that it not be used to prevent biopsy when breast biopsy is otherwise indicated. This is because, based on our research experience, we believe a negative T-Scan study should not negate the findings for biopsy shown on mammography, MRI or ultrasound. (3) When used beyond the FDA approved indications, this information will not be used in clinical decision making. The results of EIS are usually used independent of US information; we will combine the results with US information.

Women who have a breast biopsy following T-Scan will have special pathology tests of cell density and lesions vascularity. These tests are performed in some, but not other cases as part of routine pathology analysis of biopsy specimens. These special studies will be requested in all cases within this study and if the extra tests are not clinically indicated will have the extra charges covered by the grant. We do not expect that these tests of lesion cellularity and vascularity done specifically for this study will have any effect on the clinical decisions made for patient care. In some cases these special studies are used to assist in the diagnosis of uncertain pathology lesions. When selected for clinical diagnosis by the pathologist reviewing the clinical biopsy, they may result in more accurate classification of the tumor which could affect patient care.

Section Four: Selection of Subjects and the Informed Consent Process

1. Indicate whether this project involves any of the following subject populations?
   - ☐ Children (Children are defined by District of Columbia law as anyone under age 18.)
   - ☐ Prisoners
   - ☐ Pregnant women
   - ☐ Cognitively impaired or mentally disabled subjects
   - ☐ Economically or educationally disadvantaged subjects

If you indicated any of the above, in the space below, please describe what additional safeguards will be in place to protect these populations from coercion or undue influence to participate. (Use additional sheets as needed.)

NA

1. Describe how subjects will be recruited and how informed consent will be sought from subjects or from the subjects' legally authorized representative. If children are subjects, discuss whether their assent will be sought and how the permission of their parents will be obtained. Use additional sheets as needed.

Patients attending the Ourisman Breast Health Center for diagnostic evaluation of suspect lesions will be approached by one of the clinical investigators to determine if they are will to consider participation in this clinical trial. If they express initial interest, the research associate or one of the clinical investigators will explain the procedure to them, will review the consent form and if they are agreeable proceed with the study either at that time or at a later scheduled time.

1. Will subjects receive any compensation for participation in cash or in kind?
   - ☐ Yes. If so, please describe amount or kind of compensation in the space below.
   - ☐ No.

Most participants will receive no compensation for participation.

Up to 10 pre-menopausal participants with T-Scan positive findings will be asked to return weekly for four to eight weeks to study the effect of the menstrual cycle on T-Scan positive findings that are not due to cancer to assess the effect of the menstrual cycle on the T-Scan findings. They will be paid $25 for each session.

1. Will any finder's fees be paid to anyone, including physicians?
   - ☐ Yes. If so, please describe the amount below.
   - ☐ No.

Section Five: Privacy and Confidentiality of Data and Records

1. Will identifiable, private, or sensitive information be obtained about target the subjects or other living individuals? Whether or not such information is obtained, describe the provisions to protect the privacy of subjects and to maintain the confidentiality of data. Use additional sheets as needed.

Identifiable information will be obtained on the volunteers for this study. All images will be initially labeled with the patients name and hospital number since findings from these studies could be required for patient care needs (in the case of finding an unexpected lesion that requires biopsy). When the T-Scan is used within its FDA approved indications, a report of the findings will be placed in the patient's medical record. Ultrasound images will be stored on the MedStar Georgetown Hospital Ultrasound systems and in the Georgetown Ultrasound electronic storage system. They will be covered by the same confidentiality requirements as used by MedStar Georgetown Hospital uses for its Medical Records. T-Scan records will be maintained on the T-Scan system computer. This is a non-

networked computer. Network connections can however be established for remote equipment maintenance and service. Currently, these activities are handled over phone modem connections. We will establish a password for access to information on the T-Scan system.

For other purposes, files containing information will be maintained in a locked facility and will be filed under a sequential case study number.

Computer records used in analyzing the data obtained in this study will be maintained behind the firewall of the Imaging Science and Information Systems Center of the Department of Radiology.

I certify that the information furnished concerning the procedures to be taken for the protection of human subjects is correct. I will seek and obtain prior approval for any modification in the protocol or informed consent document and will report promptly any unexpected or otherwise significant adverse effects encountered in the course of this study.

I certify that all individuals named as consultants or co-investigators have agreed to participate in this study.

Signature of Investigator	Date 8/16/01
Department Chair: ☒ Approved ☐ Disapproved Signature of Department Chair	Date 8/17/01

If more than one department or administrative unit is participating in the research and/or if the facilities or support of another unit, e.g., nursing, pharmacy, or radiation therapy, are needed, then the chair or administrative official or each unit must also sign this application.

Authorized Signature and Title MD	Date 8/17/01
Authorized Signature and Title	Date
Authorized Signature and Title	Date

Initials of Volunteer _____. Initials of Witness _____

GEORGETOWN UNIVERSITY
Consent to Participate in Research

Project Name Electrical impedance imaging of the breast: Correlation with MRI, US, Sestamibi and histology with measures of cell proliferation and vascular density.

Project Director Matthew Freedman, MD, MBA

Principal Investigator Matthew Freedman, MD, MBA **Telephone** 202-784-3417, 202-687-7948

Sponsor Friends...you can count on Foundation.

The Georgetown University Institutional Review Board has given approval for this research project. For information on your rights as a research subject, call the Institutional Review Board office: 202-687-1506.

Introduction

You are invited to consider participating in this research study. We will be evaluating a method of breast cancer diagnosis that uses electrical impedance imaging. This form will describe the purpose and nature of the study, its possible risks and benefits, other options available to you, and your rights as a participant in the study. Please take whatever time you need to discuss the study with your physicians, hospital personnel and your family and friends. The decision to participate or not is yours. If you decide to participate, please sign and date the last line of this form and initial each page.

The research is being sponsored by *the US Army Breast Cancer Research Program. US Army Breast Cancer Research Program* is called the sponsor and *Georgetown University*, is being paid by *the US Army Breast Cancer Research Program* to conduct this study with *Matthew Freedman, MD, MBA* as the primary investigator.

Background and purpose of the study

We will be comparing the findings of the TransScan T-Scan Breast Diagnostic System to those of mammography and ultrasound, and in some volunteers to breast MRI and pathology findings.

Total number of subjects

About 100 people will take part in this study. Participants in the study are referred to as "subjects." 100 subjects will be participating at this site.

General plan of this study

How your diagnostic evaluation will be determined in this study

If you agree to participate, you will have a T-Scan study of your breast or breasts. If there is a finding on your mammogram, or if you have a positive finding on the T-Scan, you will also have an ultrasound examination of the location or locations in your breast that show positive findings. We will also use a copy of your mammogram in this study. If you have an MRI of your breasts, we will also use a copy of the MRI in this research. If you have a breast biopsy, we will also use that biopsy in this research. In some cases, if you have a biopsy, we will ask the pathologist to do special pathology studies of the biopsy tissue.

Length of the study for each subject

We expect that you will be in the study for approximately 1 year. You will have an initial study that will take less than an hour. In one year, we may contact you to find out the results of your next annual mammogram. We request your permission to directly obtain the results from your next mammogram if it is obtained at the Ourisman Breast Health Center of Georgetown University and the Lombardi Cancer Center.

A small number of volunteers will be asked, based on the findings on the T-Scan, to also agree to additional T-Scan and ultrasound examinations. These are intended to study the effect of the menstrual cycle on T-Scan findings. If you agree to participate in this additional study, we will ask you to return each week for four to eight weeks. If you qualify for this additional study, we will explain the procedure and provide you with an additional consent form.

Possible benefits of participating in the study

You might benefit from this study if we find a cancer that could not be identified on your mammogram. We consider the chance of this happening very unlikely (less than 1 in 100). However, we cannot guarantee that you will experience medical benefits from participating in this study. Others may benefit in the future from the information we obtain while you are in this study.

If you are taking any over-the-counter drugs, herbal supplements, etc. which you have purchased from the drug store, grocery store, etc., you should advise your physician.

Possible side effects and other risks of participating in the study

You may experience some side effects as a result of the experimental diagnostic studies you receive in this study.
About one in every five women who participates feels a tingling from the T-Scan system. They have told us that this is not uncomfortable.

The T-Scan system and its predecessor devices have been used more than 20,000 without complication. The device is FDA approved. We therefore do not anticipate any complications from the use of this device.

We will take reasonable safeguards to minimize known and potential risks but unknown and/or unanticipated side effects might occur.

Other risks of this study include a risk of misdiagnosis. In this study, you will have a breast ultrasound of specific areas of your breast that did not show an abnormality on mammography, but may show an abnormality on the T-Scan study. We know that most of these T-Scan findings are not clinically important, but to be certain, we will be obtaining ultrasound examinations of those areas that are T-Scan positive. There is a risk that the ultrasound will show an abnormality that could be cancer and that based on the ultrasound, we will advise you to have a biopsy of the abnormality. Using the standard ultrasound criteria for recommending biopsy, we would expect that only one of every five biopsies would show cancer and that the others would show no evidence of cancer. Thus there is a risk that we will find something that requires biopsy, but is not due to cancer.

Who can participate

This study is designed for women age 35 or older who have a suspect area identified on their screening mammogram and for whom additional evaluation has been recommended. Your suitability for this study will be determined by radiologists evaluating your mammogram in the Ourisman Breast Health Center based on criteria determined by Matthew Freedman, MD, MBA

Who cannot participate: You should not participate if you have any implanted electrical device such as a cardiac pacemaker or a pain control electrical stimulator.

Avoidance of Pregnancy

There is no information concerning the safety of the use of the T-Scan device during pregnancy. The procedures used in this study may be unsafe for an unborn baby, an infant, sperms, and eggs. If you, as a subject of study, are a woman of child bearing potential, you must agree to avoid pregnancy during your participation in this study and for *three months* after the completion of the study. If you do become pregnant during the study you should immediately notify Dr. Matthew Freedman at 202-784-3417. In addition, if you are already pregnant or are breast feeding, you cannot participate in this study. If there is any potential that you are pregnant and you will to participate, we will perform a pregnancy test. The research project will cover this cost.

Other treatment options

If you do not participate in this study, the following options are available to treat your illness/condition: Additional mammography images, standard ultrasound, MRI, breast biopsy.

Confidentiality of the data collected during the study

Every effort will be made to keep your medical records confidential as well as other personal information that we gather during this study. However, we cannot guarantee absolute confidentiality.

Whenever data from this study are published, your name will not be used.

Individuals from the Georgetown University IRB, Georgetown University Hospital and Medical Center, the U.S. Food and Drug Administration, the US Army Medical Research and Materiel Command may look at medical and research records related to this study, both to assure quality control and to analyze data. We will disclose personal information about you to others as required by law.

A record of your participation in this project will be maintained by the US Army in its research database. The U.S. Army will maintain a confidential data base containing your name, address, social security number, study name and dates. The intent of the data base is for your protection: first to readily answer questions concerning an individuals participation in research sponsored by the US Army Medical Research and Materiel Command (USAMRMC) and, second, so that the USAMRMC can ensure that research volunteers are adequately warned of any newly identified risks or hazards that may be related to the research performed. This data base will be maintained by the USAMRMC for at least 75 years.

If you are a member of the US Military, special rules on confidentiality apply to you. Complete confidentiality cannot be promised, because information bearing on your health may be required to be reported to appropriate medical or command authorities.

Data security

Information about your participation in this study is stored in a computer. The following precautions are taken to protect it from unauthorized disclosure, tampering, or damage: 1. Your medical images and reports are maintained in the computerized storage facilities of MedStar Georgetown Hospital and are subject to their controls. 2. The T-Scan images are maintained on the computer attached to the imaging system. This computer is not linked to any network and the system is passwork protected. 3. The data record of your participation is kept in a secured computer protected by a firewall at the Imaging Science and Information System Research Center of Georgetown University.

Only authorized users will have access.

New findings

Throughout the study, we will tell you about new information we receive about diagnostic tests that may be appropriate for you, about the methods under research in this study, and any information that may affect your interest in remaining in the study.

Costs to you for participating

Qualified study subjects will not have to pay for the research imaging studies. You or your insurance company will have to pay for the standard medical care you receive. If a lesion requiring biopsy is found during the ultrasound examination that is part of the study, you or your insurance company will have to have for this biopsy and care.

Payments to you for participating

Qualified study subjects will not be paid for participating in this study. Some participants may be asked to come back several times for a series of studies with T-Scan to determine whether menstrual changes affect the T-Scan. In that case, $25 will be paid per visit.

Commercial Interest

The investigators, Georgetown University and MedStar Georgetown Hospital have no commercial interest in the T-Scan system or the company, TransScan Ltd that manufacturers it.

Compensation in case of injury

We will make every effort to prevent study-related injuries and illnesses. If you are injured or become ill while you are in the study and the illness or injury is due to your participation in this study, you will receive emergency medical care. The costs of this care will be charged to your health insurer. This is a project funded by the US Army Medical Research and Materiel Command. Should you be injured as a direct result of participating in this research project, you will be provided medical care, at no cost to you, for that injury. You will not receive any injury compensation, only medical care. You should also understand that this is not a waiver or release of your legal rights. You should discuss this issue thoroughly with the principal investigator before you enroll in this study. Your insurance will be billed for the cost of this medical care, but you will not be responsible for any costs not covered by your insurance. No funds are available from Georgetown University, Georgetown University Hospital or their affiliates, the District of Columbia government or the federal government to compensate you for a study-related injury or illness. Other than the medical care that may be provided and any other payment specifically stated in the consent form, there is no other compensation available for your participation in this research.

Your rights as a participant in the study

Participation in this study is entirely voluntary. You have the right to leave the study at any time. Leaving the study will not result in any penalty or loss of benefits to which you are entitled. Should you decide to leave the study, the procedure is the following: Notify Matthew Freedman, MD, of your desire to no longer participate in the study. If your decision is made during the imaging, you should inform the technologist or physician performing the imaging studies that you wish them to stop the study and they will stop the imaging. Should you decide not to participate or to withdraw, your medical care will not be affected nor will your relations with your physicians, other personnel and the hospital or university. Your care, however, may subsequently be managed by different researchers or physicians.

Problems and questions

Call Dr. Matthew Freedman at 202-784-3417 days or the radiologist on duty at night if you have questions about the study, any problems, unexpected physical or psychological discomforts, any injuries, or think that something unusual or unexpected is happening. The fastest way to contact the radiologist on duty is to contact the Radiology Resident on duty, either directly by page at 202-668-7613 or through the page operator at 202-784-7243.

Call the Georgetown University IRB office at 202-687-1506 with any questions about your rights as a research subject.

Withdrawal by investigator, physician, or sponsor

The investigators, physicians or sponsors may stop the study or take you out of the study at any time should they judge that it is in your best interest to do so, if you experience a study-related injury, if you need additional or different medication, or if you do not comply with the study plan. They may remove you from the study for various other administrative and medical reasons. They can do this without your consent.

Investigator's statement

I have fully explained this study to the subject. I have discussed the procedures and treatments, the possible risks and benefits, the standard and research aspects of the study, and have answered all of the questions that the subject and the subject's family members have asked.

Signature of investigator _____ Date _____

Subject's consent

I have read the information provided in this Informed Consent Form (or it was read to me by _____). All my questions were answered to my satisfaction. I voluntarily agree to participate in this study.

[Upon signing, you will receive a copy of this form, and the original will become part of your medical record.]

Signature of witness _____ Date _____

Your signature _____ Date _____